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Adaptation to potassium

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In vertebrates, the development of complex and efficient mechanisms for avoiding potassium intoxication might be predicted from a simple consideration of their chemical anatomy. The proper function of excitable membranes depends on a low concentration of potassium outside of the cell. On the other hand, potassium is the major ionic constituent of intracellular fluid; it therefore accompanies calories in almost every form of food. Animals that alternate starvation with periods of gorging themselves must therefore be able to adapt to sudden large exogenous loads of potassium in order to avoid potassium intoxication.

The adaptive capacity to avoid potassium intoxication was first described by Thatcher and Radike [1] who noted that rats receiving increasing doses of potassium chloride by stomach tube over a period of twelve days became resistant to an oral dose of potassium normally lethal in nonadapted rats; they termed this response "potassium tolerance." The same phenomenon was soon confirmed in man [2] and dog [2, 3] where it was linked to the excretion of potassium in the urine in excess of the amount filtered by the glomeruli. Potassium secretion by the kidneys was observed only in those experimental subjects that had been previously loaded with potassium. Similar observations are available in other animal species, suggesting that the phenomenon is widespread. Cattle and sheep, normally fed a diet with a high content of potassium, regularly and rapidly secrete potassium in the urine when they are challenged with an i.v. infusion of potassium salts [4, 5]. It has been suggested that their chronically high dietary potassium is responsible for the tolerance to potassium they exhibit.

An adaptive increase in potassium secretion by renal tubular cells is often a feature of renal insufficiency. Potassium homeostasis is usually well maintained in chronic renal failure, even though the reduction in functional nephron mass results in a relative excess of potassium ions that need to be excreted. In rats with renal insufficiency induced by 75% nephrectomy, the urinary excretion of potassium per unit of kidney wt following i.v. administration of potassium chloride is brisk and comparable to that observed only after prolonged dietary loading with potassium in normal rats [6, 7]. A similar observation had been previously made in dogs by Schultze et al [8]. These authors studied animals with dual urinary bladders and a 75% infarcted kidney. They observed that the urinary excretion of potassium by the remnant kidney increased rapidly after removal of the contralateral intact organ, and that its efficiency in removing potassium increased as uremia was established. These experiments suggest that in chronic renal failure potassium tolerance depends heavily on the ability of the remaining hypertrophied nephrons to develop the capacity to secrete potassium.

A second mechanism that might contribute to the maintenance of potassium homeostasis has been described by Hayes, McLeod, and Robinson [9] in uremic patients. These authors observed that the percentage of the dietary potassium load excreted by uremic patients in the stool averaged almost threefold that of normal subjects. Since potassium is dissolved in stool water, however, when there is no diarrhea or liquid stools, the contribution of stool potassium to the excretion of excess dietary potassium is likely to be limited. For further information regarding the maintenance of potassium homeostasis during renal insufficiency, the reader is referred to the review by C. van Ypersele de Strihou in this symposium.

A third mechanism for potassium tolerance has also been proposed. Alexander and Levinsky [10] observed that the plasma potassium concentration of potassium-adapted rats did not increase as much as that of nonadapted rats when challenged with an acute potassium load immediately after bilateral nephrectomy. They also observed that prior adrenalectomy abolished the adaptation and that stimula-

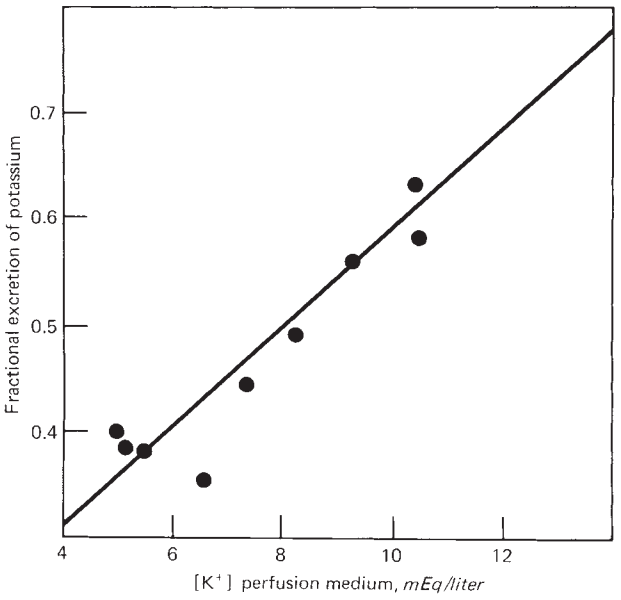

Fig. 1. *Fractional excretion of potassium in an isolated perfused rat kidney plotted against increasing concentration of potassium in the perfusate.* As perfusate potassium concentration is gradually increased, the fractional excretion of potassium increases approximately two-fold. (Reproduced with permission from *J Clin Invest.*)

tion of endogenous aldosterone secretion by feeding the animals a low sodium diet resulted in adaptation to potassium loads. Adrenalectomized rats given large doses of deoxycorticosterone acetate also demonstrated adaptation. They concluded that potassium adaptation occurred because of a chronic increase in aldosterone secretion which mediated the uptake of potassium into the tissues.

Renal adaptation to potassium. Exogenous administration of potassium salts in rat, dog, and man is followed by a rapid increase in the renal excretion of potassium [2, 3, 6, 7, 11, 12] associated with a variable rise in the concentration of potassium in plasma. This response appears to be intrinsic to the kidney as demonstrated by studies of the isolated perfused kidney of the rat. In Figure 1, fractional excretion of potassium in an isolated perfused rat kidney is plotted against increasing concentration of potassium in the perfusate. As perfusate potassium concentration is gradually increased from 5 to 10 mEq/liter, the fractional excretion of potassium increases approximately two-fold [13]. Thus, the kidney has an intrinsic ability to respond to increased loads of potassium by excreting more potassium into the urine.

Animals conditioned to a high intake of potassium in the diet regularly secrete large amounts of potassium in the urine [2, 6, 7] even when not challenged by i.v. potassium loads. This adaptive secretion of potassium can be demonstrated *in vitro* as well. Isolated perfused kidneys obtained from rats chronically loaded with potassium secrete potassium into the urine in excess of the amount filtered, over a wide range of potassium concentrations in the perfusate (Fig. 2) [13]. Thus, the capacity to secrete potassium in large amounts is also an intrinsic characteristic of the kidney, acquired during the process of potassium adaptation and evident in the isolated organ perfused with an artificial medium outside of the range of extrarenal influences.

The mechanism by which the kidney secretes potassium into the urine involves the activity of the cells of the distal nephron [15]. The processes by which the tubular cells do this are discussed in detail by F. S. Wright in another section of this symposium. At least three processes have been involved as controlling the movement of potassium across the distal tubule into the lumen. The experiments of Giebisch, Boulpaep, and Whittenbury [16] have shown that the secretory movement of potassium into the lumen of the distal nephron involves the active peritubular uptake of this ion, and passive diffusion into the lumen down the chemicals gradient. The active peritubular uptake of potassium controls the size of the intracellular potassium pool which determines the gradient for the diffusion of potassium into the lumen [17]. Kinetic studies *in vivo* [18] have shown that after potassium-loading there is an increased peritubular uptake of potassium, resulting in a rise in the intracellular po-

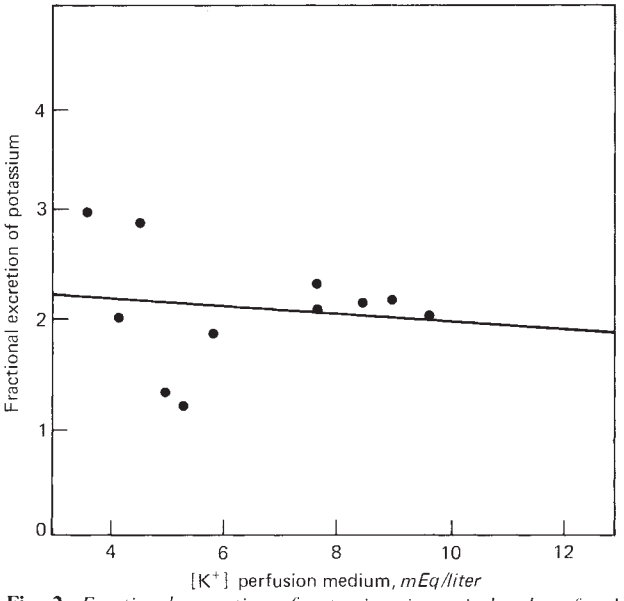

Fig. 2. *Fractional excretion of potassium in an isolated perfused kidney obtained from a potassium-adapted rat plotted against increasing concentration of potassium in the perfusate.* Net secretion of potassium is observed over a wide range of potassium concentrations in the perfusate. (Reproduced with permission from *J Clin Invest.*)

tassium pool. Conversely, during potassium depletion movement of potassium into the cells across the peritubular membrane is decreased with a reduction in the intracellular potassium pool. The rate of flow of the tubular fluid along the distal nephron also controls the rate of potassium secretion, inasmuch as increases in flow rate are accompanied by increases in the rate of secretion of potassium [19]. There is reason to believe, however, that the effect of flow on potassium secretion is dependent on the size of the intracellular potassium pool, since increases in flow are not accompanied by increases in potassium secretion in states of potassium depletion [20]. Another factor that can participate in the control of potassium secretion is the transmural potential difference in the distal nephron. Transepithelial potential difference in the distal tubule has been found to be higher in animals loaded with potassium than in pair-fed controls [15, 21], suggesting that the driving force for potassium excretion from blood to lumen is increased. Conversely, in potassium-depleted animals the potential difference (PD) across the distal tubule has been found to be decreased [7]. Thus, the PD across the distal nephron changes in parallel with potassium secretion and could be a major factor in controlling the rate of distal potassium secretion. In the experiments of Wright et al [15], however, the acute infusion of potassium chloride did not increase the PD but actually decreased it in potassium-adapted rats, a circumstance in which potassium secretion is stimulated. This experiment indicates that the transtubular PD itself is not the principal driving force for the movement of potassium from the peritubular space into the distal tubular lumen. From this brief description of the mechanism of potassium secretion by the kidney, it is apparent that the size of the intracellular potassium pool and its determinant, the active peritubular uptake of potassium, are major factors controlling the secretion of potassium into the urine.

Role of Na-K-ATPase in potassium adaptation. The peritubular uptake of potassium in exchange for intracellular sodium is presumably mediated by sodium-potassium-activated adenosine triphosphatase (Na-K-ATPase). The elegant experiments of Schmidt and Dubach have shown that this enzyme is present primarily on the basolateral membranes of renal tubular cells and that its activity is especially high in cells of the distal nephron [22] (i.e., the thick ascending limb of Henle's loop, the distal convolution, and the collecting duct). It is natural to suggest that the impressive adaptation to potassium exhibited by the kidney might be mediated by changes in the specific activity of Na-K-ATPase. Indeed, measurements of Na-K-ATPase in potassium-adapted animals show a selective increase of this enzyme in renal tubular cells [7, 23]. An increase of three- to four-fold in the normal dietary content of potassium produced an increase in the activity of the enzyme limited to the outer medulla of the kidney (Fig. 3). Further increase in dietary potassium results in increases in enzyme activity in the renal cortex and inner medulla and papilla, as well as in the outer medulla (Fig. 4) [7, 13, 23]. Continuing the exposure to a high load of potassium for a longer period of time increases Na-K-ATPase activity in all portions of the kidney [23]. The increase in Na-K-ATPase activity is not observed in the kidney until three to four days after the initiation of potassium-loading, suggesting that this adaptive response requires a series of metabolic steps including the formation of new protein (CHARNEY, SILVA, EPSTEIN, unpublished observations).

The relative increase in potassium excretion per nephron observed during renal insufficiency is also accompanied by changes in Na-K-ATPase activity in the remnant kidney [6]. In partially nephrectomized rats eating a diet with a normal content of potassium, the activity of Na-K-ATPase in both cortex and me-

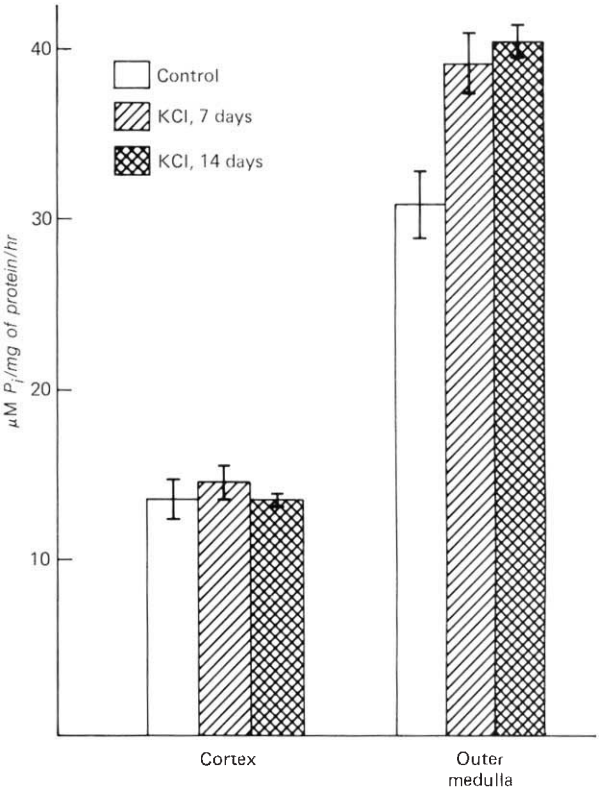

Fig. 3. *Effect on renal Na-K-ATPase of increasing the dietary load of potassium three- to four-fold.* The change in enzymatic activity is limited to the outer medulla of the kidney. (Reproduced with permission from *J Clin Invest.*)

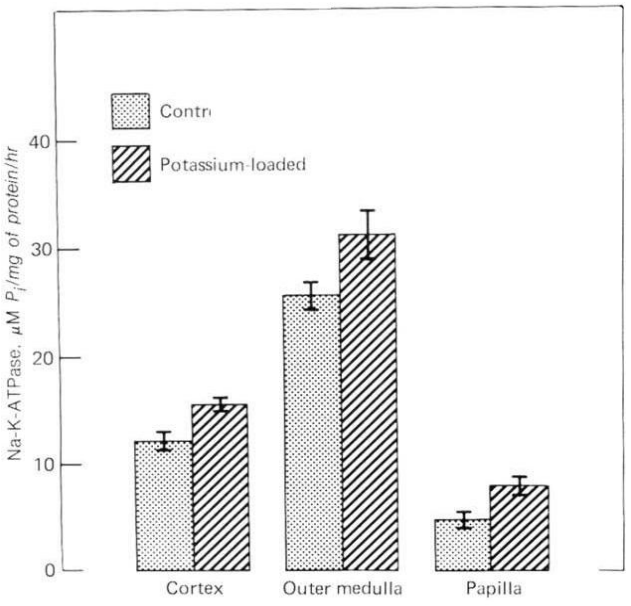

Fig. 4. *Effect on renal Na-K-ATPase of increasing the dietary load of potassium ten-fold for seven days.* The increase in enzyme activity is observed in all portions of the kidney. (Reproduced with permission from *J Clin Invest.*)

dulla of the remnant kidney is elevated above that of normal controls. When the fractional excretion of potassium (potassium clearance/inulin clearance) was reduced in such animals by reducing its intake, renal Na-K-ATPase activity was found to be essentially similar to that of controls. Thus, the increase in Na-K-ATPase seen in compensatory renal hypertrophy after partial nephrectomy is due, at least in part, to a relative increase in the excretory load of potassium [6].

One way to evaluate the role of Na-K-ATPase in potassium excretion is to examine the effects of specific inhibition of the enzyme with cardiac glycosides. For example, strophanthidin decreases the rate of urinary potassium excretion in the kidney of the chicken, in which urinary excretion of potassium had been stimulated by the simultaneous infusion of potassium into the renal portal vein [24]. Unfortunately, most experiments in which ouabain has been administered *in vivo* in mammals cannot be adequately evaluated because doses far below those needed for complete inhibition of renal Na-K-ATPase have to be given, even when delivered directly into the renal artery, in order to avoid lethal cardiac effects. For this reason the isolated perfused kidney has been used to study the effects of ouabain inhibition of Na-K-ATPase, without the complication of extrarenal toxicity. Bowman, Dolgin, and Carlson, utilizing the isolated perfused rat kidney preparation, showed that ouabain depresses potassium excretion [25]. Figure 5 shows the effect of ouabain, 4 mM, on the urine to plasma potassium ratios of an isolated perfused kidney obtained from a normal rat and another from a potassium-loaded rat. In both kidneys the urine to plasma potassium ratio is sharply reduced and urinary excretion of potassium was reduced to approximately the same level [13]. The sharp reduction in potassium excretion after the blockade of renal Na-K-ATPase with ouabain supports the contention that this enzyme mediates the secretory transport of potassium under normal conditions and participates in the renal adaptation to potassium-loading.

Influence of mineralocorticoids. Deoxycorticosterone acetate (DOCA) was found by Thatcher and Radike [1] to be instrumental in preadapting animals prior to potassium-loading, confirming a previous demonstration that DOCA protected mice from potassium-poisoning [26]. Berliner, Kennedy, and Hilton performed analogous experiments in dogs but found that they could not interpret the results because the animals became potassium-depleted after chronic administration of the mineralocorticoid [2]. It is now clear that aldosterone increases Na-K-ATPase activity in the kidney of rats in a way very similar to the effect of potassium-loading. The first and most striking increase in Na-K-ATPase produced by aldosterone is seen in the renal outer medulla [27]. Since potassium-loading stimulates aldosterone secretion [28, 29], it is tempting to

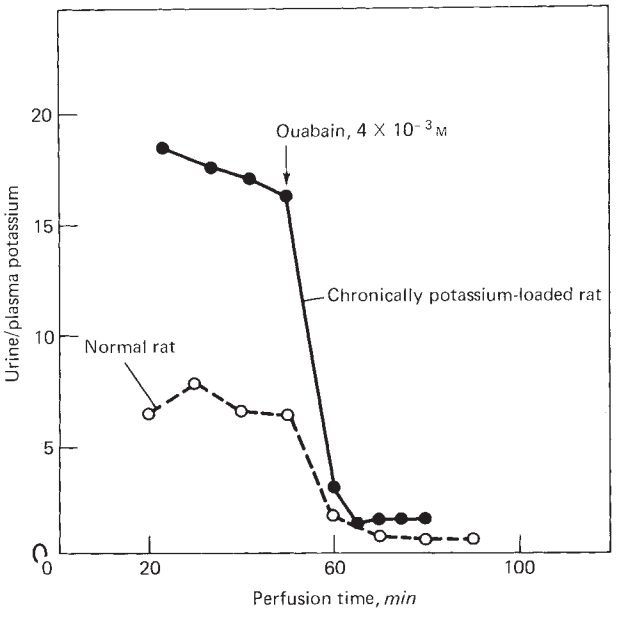

Fig. 5. *Effect of ouabain (4 mM) on urine to plasma potassium ratios in an isolated perfused kidney obtained from a normal rat and another from a potassium-loaded rat.* Urinary potassium excretion decreases dramatically after the addition of ouabain. (Reproduced with permission from *J Clin Invest.*)

speculate that the effect of potassium on renal Na-K-ATPase is mediated actively via aldosterone. Certain facts, however, stand in the way of this interpretation. A powerful stimulus for aldosterone secretion is sodium deprivation, yet this experimental maneuver has never been shown to modify the activity of renal Na-K-ATPase [23, 30, 31]. An even more compelling argument against aldosterone as the sole cause of the increase in enzyme activity is that potassium-loading in adrenalectomized rats increases the activity of Na-K-ATPase in a way entirely similar to that seen in intact rats. Aldosterone would seem to be excluded as the mediator of the increase in Na-K-ATPase activity in such experiments. Since potassium-loading in adrenalectomized animals tends to be lethal, the latter experiments were done while the rats were kept on a small maintenance dose of DOCA [23]. Thus, potassium loads appear to be able to elicit an increase in Na-K-ATPase activity in the kidney that is independent of aldosterone secretion, although a permissive effect of mineralocorticoids cannot be excluded at the present time.

Location of potassium adaptation within the nephron. The experiments of Wright et al [15] show that the site within the nephron where there is increased potassium secretion after potassium adaptation varies with the way in which adaptation was induced. When potassium adaptation follows chronic dietary potassium-loading, potassium secretion along the distal tubule increases markedly after potassium chloride infusion, with no further addition of potassium to the urine beyond the distal convolution. By contrast, when potassium adaptation is produced by depriving the animal of sodium, the amount of potassium added to the urine along the distal tubule during infusions of potassium chloride was only slightly higher than those in the control animals, but a large increment of potassium was added to the urine between the distal tubule and the final urine. This implies that the collecting duct participates in potassium adaptation after sodium deprivation. The role of the collecting duct in potassium secretion has been extensively studied [17, 32, 33] by comparing the fractional potassium excretion in end distal and final urine. The authors of these studies concluded that the collecting ducts are not a major site for potassium secretion in the rat. On the other hand, direct studies of potassium excretion by the papillary collecting duct in the hamster *in vivo* showed potassium secretion in this nephron segment [34]. Studies in isolated segments of cortical collecting duct in the rabbit also show that this portion of the nephron is capable of adding potassium to the urine [35]. The experiments of Diezi et al in the papillary collecting duct of the rat failed to demonstrate net potassium secretion consistently in potassium-loaded animals. Nevertheless, after finding net secretion of potassium in 8 out of 13 animals studied, they concluded that the epithelium of the collecting duct is potentially capable of significant potassium secretion [36]. Bank and Aynedjian [37], comparing the excretion of potassium in end distal and final urine, observed that in normal rats, infusions of potassium chloride are followed by increases in urinary potassium beyond the distal tubule. More importantly, they found that in 75% nephrectomized animals with either normal or elevated plasma potassium, potassium was added to the urine at a point distal to the end of the distal tubule. Only when potassium was eliminated from the diet and plasma potassium fell was secretion of potassium by the collecting duct not observed.

After potassium-loading, Na-K-ATPase activity is increased in the inner (white) medulla or papilla of the rat kidney traversed by the papillary collecting ducts, as well as in the outer (red) medulla and cortex [7, 13]. Increased uptake of potassium by the collecting duct cells across their peritubular membranes might induce activation of the enzyme in this location. Removal of the white papilla from kidneys of potassium-loaded rats eliminates net secretion of potassium when these kidneys are perfused *in vitro,* suggesting that the terminal collecting ducts secrete potassium in situations of potassium surfeit [13]. Similarly, in experiments in rats *in vivo,* papillectomy abolishes the increased potassium excretion observed in partially nephrectomized animals [38]. While it seems likely that secretion by the distal convoluted tubule contributes to potassium excretion, a critical role in the secretion of potassium and in determining the final composition of the urine depends, at least in the rat, on the cells of the collecting duct.

Extrarenal potassium adaptation: Excretion of potassium by the colon. Both potassium-loading [39] and renal insufficiency [9] are accompanied by an increase in the excretion of potassium into the colon. Thus, the colon participates in overall potassium homeostasis by increasing the excretion of potassium whenever there is a surfeit of this cation.

The secretion of potassium by the colon is thought to be modulated by aldosterone. In patients with primary hyperaldosteronism there is an increased secretion of potassium into the colon [40]. The administration of aldosterone increases the secretion of potassium and reabsorption of sodium by the normal human colon [41, 42]. These effects are analogous to those observed in the distal tubule of the kidney.

Potassium is thought to be transported passively along negative electrical gradients generated by the

active sodium transport across the mucosa of the colon [43, 44] in a fashion resembling the movement of potassium across the cellular epithelium of the distal nephron [16]. Active secretion of potassium, however, has also been suggested [45].

Na-K-ATPase is located in the basolateral membranes of the cells lining the mucosa of the colon [46]. The activity of the enzyme in the mucosa of the colon rises in response to potassium-loading in much the same way as renal Na-K-ATPase does (Fig. 6) [47]. An important difference between the Na-K-ATPase response in the colon and the kidney is that the response of colonic mucosa Na-K-ATPase to potassium-loading is abolished by adrenalectomy. The suggestion that Na-K-ATPase mediates the uptake of potassium into the cells of the mucosa of the colon is sustained by the observation that ouabain markedly diminishes the short circuit current in the rat colon [48] at concentrations known to inhibit Na-K-ATPase *in vitro* [49]. Thus, the response of the mucosa of the colon to potassium-loading may be dependent on the increased activity of Na-K-ATPase induced by the rise in secretion of aldosterone evoked by this cation. In this respect it is worth mentioning that Hayes et al [9] considered the possibility that the increased colonic excretion of potassium seen in renal insufficiency patients was due to aldosterone, but they failed to inhibit it with spironolactone. Although the doses they used may have been insufficient, this finding has been confirmed with high spironolactone doses in anephric patients. Additionally, the administration of DOCA to anephric patients with low ambient aldosterone levels failed to increase fecal potassium excretion (SUGARMAN A, BROWN R, personal communication).

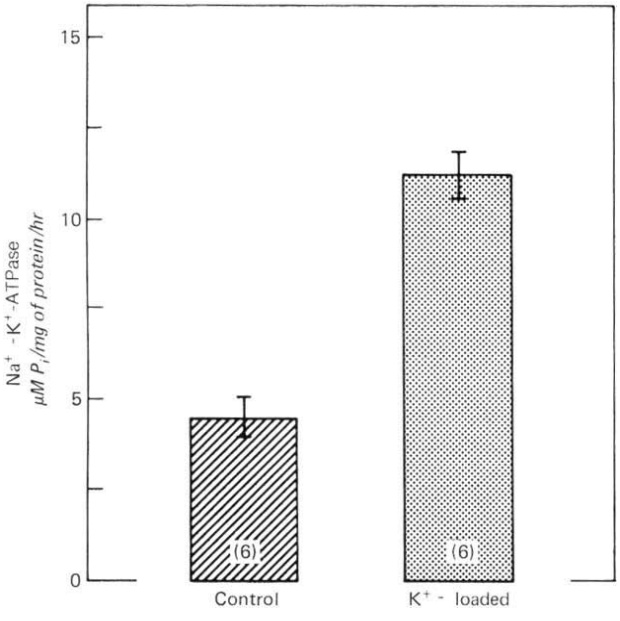

Fig. 6. *Effect of potassium-loading on the activity of Na-K-ATPase in the mucosa of the colon in the rat.* The animals were fed a diet containing ten times the normal amount of potassium for seven days.

Extrarenal potassium adaptation: Uptake of potassium into the tissues. The oral or i.v. administration of exogenous potassium is followed by rapid uptake of this ion into the tissues, so that the initial volume of distribution of an i.v. potassium load in normal subjects approximates the volume of body water [50, 51]. Alexander and Levinsky found that the plasma potassium concentrations rose significantly less after a potassium chloride load in animals previously fed large amounts of potassium than those animals that had been eating a normal diet [10], presumably because of increased uptake into the tissues. They also observed that this phenomenon could be reproduced in the absence of kidneys, was abolished by prior adrenalectomy, and could be reproduced by administration of exogenous mineralocorticoids or stimulation of endogenous secretion of aldosterone by sodium deprivation. They concluded that potassium adaptation is mediated by increased aldosterone secretion which facilitates the uptake of potassium into one or more tissues. The demonstration of increased tissue uptake of potassium following acute loads in potassium-adapted rats, however, has not yet been precisely reproduced by other investigators [14]. In the experiments of Wright et al [15], the authors infused acute loads of potassium to potassium-adapted rats in the presence of intact kidneys, making it impossible to determine the extent of uptake of potassium by tissues other than the kidney. Schon, Silva, and Hayslett [6], in studying potassium adaptation in potassium-loaded and uremic rats, inferred an extrarenal mechanism for clearing potassium from the plasma in rats fed a high potassium diet, but not in uremic rats. Of interest is the observation that in many studies plasma potassium levels in potassium-loaded animals are significantly lower than those of their controls [10, 15, 28], while in others the plasma potassium concentration is either not different [23] or even higher [6, 29] than that of their pair-fed controls. The disparity between these different results appears to reside in the fact that in the former group of studies the animals were fasted for prolonged periods of time before their blood was sampled, while in the latter two studies, the animals were allowed free access to food and water until just prior to being killed. This suggests that the mechanisms responsible for clearing the plasma of excess amounts of potassium continue to operate and overshoot when dietary potassium administration is stopped.

An important objection to the hypothesis of extrarenal potassium adaptation by tissue buffering is that analyses of tissue potassium content by three different groups of investigators have failed to show a consistent change in tissue content of potassium in potassium-loaded animals [10, 14, 23]. Small changes in intracellular concentration of potassium might, of course, be present but remain undetectable within the limits of error of tissue analysis.

Aldosterone. Since potassium-loading is a powerful stimulus to the secretion of aldosterone by the adrenal gland [28, 52], the possibility that aldosterone mediates the extrarenal uptake of potassium into peripheral tissues should be considered. The serum potassium of patients with primary adrenal insufficiency is higher than normal, and such patients tolerate the administration of potassium salts very poorly. In the studies of Alexander and Levinsky, no adaptation to exogenous potassium loads was seen in adrenalectomized rats [10]. The administration of DOCA in large amounts was followed by extrarenal adaptation to potassium, and sodium deprivation was shown by the same authors to induce increased uptake of potassium into the tissues, presumably due to endogenous aldosterone secretion. That aldosterone might be the mediator in this process is supported by the demonstration of Adler that aldosterone is capable of increasing the uptake of potassium by muscle cells *in vitro* [53]. Laragh and Capeci [54], however, found that sodium deprivation made dogs more, rather than less, sensitive to acute potassium loads. As pointed out by Wright et al [15], the difference between these two studies may reside in the extent of the sodium depletion induced by the preparatory maneuver. The animals studied by Laragh and Capeci were severely sodium-depleted, while those studied by Alexander and Levinsky had a more moderate degree of sodium depletion. Thus, at moderate sodium depletion the animals are potassium-adapted, while at more marked depletion of sodium this adaptation is lost.

In a yet unpublished study, Sugarman and Brown have shown that the administration of either DOCA or of spironolactone failed to affect the plasma potassium rise induced by acute or chronic potassium loads given to anephric humans (SUGARMAN, BROWN, personal communication). One conclusion consistent with these studies is that mineralocorticoids are necessary for extrarenal potassium adaptation by the tissues of animals with kidney function, but plays only a minor or permissive role in the uremic or anephric state.

Insulin and glucagon. Potassium has been shown to stimulate the release of insulin *in vitro* [55] in pancreas slices or isolated islets of Langerhans, isolated pancreas [56], and isolated perfused pancreas [57], as well as *in vivo* [58]. Insulin is known to decrease the plasma concentration of potassium [59] by stimulating the uptake of potassium of muscle cells [60–63]. This suggests that the beta cells of the pancreas may participate in feedback regulation of the concentration of potassium in extracellular fluid. In dogs with experimental insulin insufficiency induced by alloxan, the rise in plasma potassium after a potassium chloride infusion was more marked than that of normal controls, and the rate of disappearance of potassium from the plasma after cessation of the infusion was slower in the diabetic than in the control animals [63]. Since in these experiments the animals had intact kidneys, and urinary excretion of potassium was not determined, the contribution of the kidneys to potassium homeostasis could not be determined. Pettit and Vick studied nephrectomized dogs [61] as well as animals with normal kidneys [62]. In both groups the rise in plasma potassium after an i.v. infusion of potassium chloride was greater in pancreatectomized animals than in those with an intact pancreas; in addition, the decline in plasma potassium after cessation of the infusion of potassium was smaller in the pancreatectomized than in the non-pancreatectomized dogs. When the kidneys were present, the rise in plasma potassium after a potassium chloride infusion was smaller, of coure, than that seen in nephrectomized animals.

Potassium not only stimulates the release of insulin by the pancreas but also increases the secretory rate of glucagon which in turn increases glucose production by the liver. Hypoglycemia after the potassium-induced secretion of insulin is thereby avoided. The pancreas thus participates in the homeostasis of potassium as a well rounded regulatory system. In addition, both insulin and glucagon may modify renal excretion of potassium. Insulin has been shown to decrease potassium excretion in the isolated perfused dog kidney [64], while glucagon may offset this effect by inducing kaliuresis [65]. This topic is described more extensively by J. Knochel in another section of this symposium.

Catecholamines. Another feedback system that may be involved in extrarenal potassium homeostasis involves the catecholamines. An increase in extracellular potassium concentration stimulates catecholamine production *in vitro* [66] and *in vivo* [67], and epinephrine has been shown to reduce the concentration of circulating plasma potassium [68–70] and increase the intracellular accumulation of this ion [71]. More recently, epinephrine and beta adrenergic agents like isoproterenol have been shown to exert a protective

action against the lethal effects of hyperkalemia induced by i.v. infusions of potassium chloride [72]. The protective action of epinephrine can be demonstrated in nephrectomized cats, indicating that the decrease in plasma potassium is due to cellular uptake of this ion and not to increased renal excretion [72]. In fact, some experimental evidence indicates that both epinephrine and norepinephrine decrease the renal excretion of potassium [73, 74]. For further information, see J. Knochel in this symposium.

The effect of catecholamines may not be due solely to a direct effect of these hormones on potassium uptake by tissues but also to their recognized effect on other hormonal systems. Epinephrine increases glucagon production by the alpha cells of the perfused rat pancreas [75] and is a potent stimulator of glucose production by the liver. Both these effects could trigger insulin release from the beta cells of the islets of Langerhans. However, epinephrine has been shown to inhibit insulin production both *in vitro* [75, 76] and *in vivo* [77]. Furthermore, the hypokalemic effect of epinephrine seen in both dog and cat is evident almost immediately, making the progressive recruitment of secondary hormonal systems less likely.

The regulation of the concentration of potassium in plasma, its movement into the intracellular space, and excretion by the kidney appear to be under the control of several hormonal systems, perhaps all interrelated with one another. These different regulatory systems seem to constitute a biological "fail-safe system" designed to maintain plasma potassium levels constant and to prevent the lethal effects of uncontrolled hyperkalemia. It is perhaps appropriate to consider in this context that hyperkalemia is seldom a problem in clinical medicine, unless the excretion of potassium is decreased while its intake is maintained. Impairment of only one of the mechanisms known to control plasma potassium levels does not ordinarily affect the plasma concentration of this ion. However, combined endocrine abnormalities such as hypoaldosteronism and diabetes mellitus [78, 79] appear especially likely to predispose to hyperkalemia. The iatrogenic equivalent of this combination is seen in diabetic patients receiving potassium sparing diuretics [80, 81]. Drugs that increase cellular egress of potassium are particularly dangerous when given to patients with diseases in whom movement of potassium out of the cell is already accelerated. Examples include the administration of succinylcholine to patients with trauma [82] or burns [83].

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